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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/619,032 | 07/19/2000 | Dennis Murphy | DIVER1120-3 | 2212 |

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FISH & RICHARDSON, PC
12390 EL CAMINO REAL
SAN DIEGO, CA 92130-2081

| EXAMINER |
|---|
| RAMIREZ, DELIA M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/619,032 | MURPHY ET AL. | |
| | Examiner | Art Unit | |
| | Delia M. Ramirez | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-13,15 and 17-27* is/are rejected.

7)☒ Claim(s) *4,14 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *925/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of the Application*

Claims 1-27 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/25/2003 has been entered.

Applicant's amendment of claims 1-5, 7-8, 14, 15, addition of claims 16-27, and a declaration under 37 CFR 1.132 by Dr. Jay Short, in a communication filed on 9/25/2003, are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### *Terminal Disclaimer*

1. The terminal disclaimer filed on 9/25/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5958751 and any patent granted on Application Number 10/114083 has been reviewed and is accepted. The terminal disclaimer has been recorded.

### *Drawings*

2. The submission of corrected Figure 5A on 9/25/2003 is acknowledged. The corrected figure is accepted by the Examiner.

***Claim Objections***

3. Claim 17 is objected to due to the recitation of "nucleic acid that hybridizes to SEQ ID NO: 3". Since hybridization occurs among molecules and SEQ ID NO: 3 is the graphical representation of the order in which nucleotides in the polynucleotide of SEQ ID NO: 3 are arranged, it is suggested that the term be replaced with "nucleic acid that hybridizes to the polynucleotide of SEQ ID NO: 3" or similar. For examination purposes, the suggested language will be used. Appropriate correction is required.

4. Claims 20-21 are objected to due to the recitation of "polypeptide comprises at least # amino acids of a portion of a sequence having at least #% amino acid identity to the polypeptide of SEQ ID NO: 4". For clarity, it is suggested that the term be amended to recite "polypeptide comprises at least # amino acids of a polypeptide having at least #% sequence identity to the polypeptide of SEQ ID NO: 4" or similar. For examination purposes, the suggested language will be used. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, Second Paragraph***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 19 is indefinite in the recitation of "method of claim 17 wherein the hydrophobic amino acid comprises…" since there is no antecedent basis for the hydrophobic amino acid. For examination purposes, it will be assumed that the term recites "method of claim 18….". Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 17, 26, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 17, 26 and 27 as amended are now directed to a method for hydrolyzing α-glycosidic bonds by using a polypeptide having α-galactosidase activity, wherein the polynucleotide encoding said polypeptide hybridizes to the polynucleotide of SEQ ID NO: 3 under conditions which the Examiner has been unable to locate adequate support for in the specification. Thus, there is no indication that a method for hydrolyzing α-glycosidic bonds by using a polypeptide having α-galactosidase activity, wherein the polynucleotide encoding said polypeptide hybridizes to the polynucleotide of SEQ ID NO: 3 under the conditions recited in the claims was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

10. Claims 3, 15, 18-24, 26, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 15, 20-24 and claims 26-27 (in part) are directed to a method for hydrolyzing α-glycosidic bonds by using a genus of polypeptides having α-galactosidase activity, wherein said polypeptides comprise at least 30 or 50 amino acids of the polypeptide of SEQ ID NO: 4 or a polypeptide

having at least 70%, 80%, 90%, 95% sequence identity to the polypeptide of SEQ ID NO: 4. Claims 18, 19 (as interpreted) and claims 26-27 (in part) are directed to a method for hydrolyzing α-glycosidic bonds by using a genus of polypeptides having α-galactosidase activity, wherein said polypeptides have the sequence set forth in SEQ ID NO: 4 with one or more conservative amino acid substitutions, wherein said conservative substitutions comprise substituting one hydrophobic amino acid for another, one polar amino acid for another, arginine residues for lysine residues, glutamic acid residues for aspartic acid residues, or glutamine residues for asparagines residues.

While the specification discloses the structure of the α-galactosidase of SEQ ID NO: 4, the specification is completely silent in regard to which fragments of 30 to 50 amino acids of the polypeptide of SEQ ID NO: 4 are required for α-galactosidase function, nor does it disclose which amino acids in the polypeptide of SEQ ID NO: 4 can be conservatively substituted and still retain α-galactosidase activity. Furthermore, since the claims are not limited as to how many conservative substitutions a polypeptide having α-galactosidase activity can have, the claims encompass an extremely large number of possible substitution combinations ($2^N$-1 where N=364) and the specification provides no clue as to which of these combinations would result in a polypeptide retaining α-galactosidase activity. In addition, the specification is silent in regard to which 30 or 50 amino acids of polypeptides of any function having at least 70-95% sequence identity to the polypeptide of SEQ ID NO: 4 are required in a polypeptide to encode an α-galactosidase.

A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The recited structural feature of the genus (i.e., the sequence of SEQ ID NO: 4 with any number of conservative substitutions, 30 or 50 amino acids of the polypeptide of SEQ ID NO: 4 or a polypeptide having 70-95% sequence identity to the polypeptide of SEQ ID NO: 4) does not constitute a substantial

portion of the genus as the remainder of the structure of any polypeptide having α-galactosidase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. The specification discloses only a single species of the genus of polypeptides (i.e., the polypeptide of SEQ ID NO: 4) required to practice the claimed method, which is insufficient to put one of skill in the art in possession of the attributes and features of the claimed invention. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 1-3, 5-13, 15 remain rejected and newly added claims 17-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for hydrolyzing α-glycosidic bonds by using the α-galactosidase of SEQ ID NO: 4, does not reasonably provide enablement for a method for hydrolyzing α-glycosidic bonds using (1) an α-galactosidase having at least 70% or 90% sequence identity to the polypeptide of SEQ ID NO: 4, (2) an α-galactosidase having at least 30 contiguous amino acids of the polypeptide of SEQ ID NO: 4, (3) an α-galactosidase having at least 30 or 50 amino acids of a polypeptide having at least 70%, 80%, 90%, or 95% sequence identity to the polypeptide of SEQ ID NO: 4, or (4) an α-galactosidase encoded by a polynucleotide which hybridizes to the polynucleotide of SEQ ID NO: 3 under the conditions recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

12. This rejection, which has been discussed at length in an Office Action mailed on 12/2/2002 and a Final Action mailed on 5/23/2003, is maintained in regard to claims 1-3, 5-13, 15 and applied to newly added claims 17-27 for the reasons of record and the reasons set forth below.

13. Applicants argue that the specification enabled the skilled artisan at the time of the invention to identify, make and use a genus of α-galactosidases to practice the claimed invention. Applicants refer to

a declaration by inventor Jay Short, who declares that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art was very high. Dr Short's declaration further states that one of skill in the art at the time of the invention could use the teachings of the specification and other protocols known in the art to screen for polypeptides having α-galactosidase activity and that while the number of samples needed to be screened may have been high, the screening procedures were routine and successful results predictable. According to Dr. Short's declaration, knowledge of the specific structural elements which correlate with α-galactosidase activity would not have been required to create variants and test them for activity. Applicants further argue that enablement is not precluded by the necessity to screen large number of compositions as long as that screening is routine. Applicants further refer to *Hybritech, Inc. v. Monoclonal Antibodies, Inc*. as support for the argument that the claimed invention is enabled even if there is a need to screen numbers of negatives to find a sample with the desired activity. In addition, Applicants present Exhibit A, which shows copies of recently issued claims in U.S. Patent No. 6593514, 6590141, 6586215, 6596926, 6586179, 6583337, 6541684, in support of the argument that genera of polynucleotides based on sequence identity have been found patentable.

14. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection in regard to claims 1-3, 5-13, 15 or to avoid the rejection of newly added claims 17-27. The Examiner acknowledges the ruling in *Hybritech, Inc. v. Monoclonal Antibodies, Inc* as well as the declaration by inventor Jay Short and agrees that enablement is not precluded by the need of screening a number of compositions as long as the screening is routine. Furthermore, the Examiner agrees that creation of variants having the structural limitations recited in the claims is routine in the art. However, the Examiner disagrees with Applicant's contention that testing the extremely large number of variants encompassed by the claims is not undue experimentation when there is no guidance or knowledge as to which are the structural elements in the polypeptide of SEQ ID NO: 4 which correlate with α-galactosidase activity. It is not routine in the art to randomly create an infinite number of variants and

test them for activity. Instead, one of skill in the art would have some knowledge or guidance as to how structure correlates with function such that a reasonable number of variants with the potentiality of having the desired function can be created and tested.

15. In addition to claims directed to a method for hydrolyzing a-glycosidic bonds with polypeptides having α-galactosidase activity which are at least 70%-90% sequence identical to the polypeptide of SEQ ID NO: 4, the claims are also directed to a method for hydrolyzing a-glycosidic bonds with (1) α-galactosidases having at least 30 contiguous amino acids of the polypeptide of SEQ ID NO: 4, (2) α-galactosidases having at least 30 or 50 amino acids of a polypeptide having at least 70%, 80%, 90%, or 95% sequence identity to the polypeptide of SEQ ID NO: 4, (3) α-galactosidases which are the result of any number of conservative substitutions to the polypeptide of SEQ ID NO: 4, and (4) α-galactosidases encoded by a polynucleotides which hybridizes to the polynucleotide of SEQ ID NO: 3 under the conditions recited. As such, the number of α-galactosidase variants encompassed by the claims is extremely large. As indicated above, the number of substitution combinations for the α-galactosidases encompassed by claims 18-19, 26-27 alone is $2^N$-1 (where N is 364, the number of amino acids in SEQ ID NO: 4), in view of the fact that the claims do not have any limitations in the number of substitutions in the polypeptide of SEQ ID NO: 4. As indicated in the Final Action mailed on 5/23/2003 and reiterated herein, the specification is completely silent in regard to which are the amino acid residues which can be substituted, deleted, or inserted in the polypeptide of SEQ ID NO: 4 to obtain structural homologs of the polypeptide of SEQ ID NO: 4 as recited in the claims which retain α-galactosidase activity. Furthermore, as indicated in the Final Action, the art as evidenced by Bork (Genome Research, 10:398-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001), clearly teaches the unpredictability of assigning function based on structural homology and how small structural changes can lead to major changes in function.

16. While the Examiner acknowledges the issued patents presented in Exhibit A, it is noted that each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the patentability of the inventions claimed in such patents would require a detailed review of the record of each individual case, which would be improper herein. Therefore, in view of the lack of information in regard to how structure correlates with α-galactosidase function, the lack of information as to which substitutions in the polypeptide of SEQ ID NO: 4 can be made without disrupting α-galactosidase activity, and the unpredictability of the art in regard to structural changes and function, one of skill in the art would have to go through the burden of undue experimentation to enable the full scope of the claimed invention. Thus, one cannot reasonably conclude that the specification provides adequate enablement for the full scope of the claimed invention.

***Double Patenting***

17. Claims 1-15 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5958751.

18. Claims 1-15 were provisionally rejected under the judicially created doctrine obviousness-type of double patenting as being unpatentable over claim 1 of copending Application No. 10/114,083.

19. In view of Applicant's submission of a terminal disclaimer filed on 9/25/2003, these rejections are hereby withdrawn.

***Allowable Subject Matter***

20. Claims 4, 14 and 16 appear to be allowable over the prior art of record but are objected to since they depend upon a rejected base claim.

***Conclusion***

21. No claim is in condition for allowance.

22. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 24, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
1600